Page 1 13:10 <golam shameem> 06/17/2004

Connecting via Winsock to STN

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LOGINID:ssspta1626gms

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

| | | |
|---|---|---|
| NEWS 1 | | Web Page URLs for STN Seminar Schedule - N. America |
| NEWS 2 | | "Ask CAS" for self-help around the clock |
| NEWS 3 | JAN 27 | Source of Registration (SR) information in REGISTRY updated and searchable |
| NEWS 4 | JAN 27 | A new search aid, the Company Name Thesaurus, available in CA/CAplus |
| NEWS 5 | FEB 05 | German (DE) application and patent publication number format changes |
| NEWS 6 | MAR 03 | MEDLINE and LMEDLINE reloaded |
| NEWS 7 | MAR 03 | MEDLINE file segment of TOXCENTER reloaded |
| NEWS 8 | MAR 03 | FRANCEPAT now available on STN |
| NEWS 9 | MAR 29 | Pharmaceutical Substances (PS) now available on STN |
| NEWS 10 | MAR 29 | WPIFV now available on STN |
| NEWS 11 | MAR 29 | New monthly current-awareness alert (SDI) frequency in RAPRA |
| NEWS 12 | APR 26 | PROMT: New display field available |
| NEWS 13 | APR 26 | IFIPAT/IFIUDB/IFICDB: New super search and display field available |
| NEWS 14 | APR 26 | LITALERT now available on STN |
| NEWS 15 | APR 27 | NLDB: New search and display fields available |
| NEWS 16 | May 10 | PROUSDDR now available on STN |
| NEWS 17 | May 19 | PROUSDDR: One FREE connect hour, per account, in both May and June 2004 |
| NEWS 18 | May 12 | EXTEND option available in structure searching |
| NEWS 19 | May 12 | Polymer links for the POLYLINK command completed in REGISTRY |
| NEWS 20 | May 17 | FRFULL now available on STN |
| NEWS 21 | May 27 | STN User Update to be held June 7 and June 8 at the SLA 2004 Conference |
| NEWS 22 | May 27 | New UPM (Update Code Maximum) field for more efficient patent SDIs in CAplus |
| NEWS 23 | May 27 | CAplus super roles and document types searchable in REGISTRY |
| NEWS 24 | May 27 | Explore APOLLIT with free connect time in June 2004 |

| | |
|---|---|
| NEWS EXPRESS | MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004 |
| NEWS HOURS | STN Operating Hours Plus Help Desk Availability |
| NEWS INTER | General Internet Information |
| NEWS LOGIN | Welcome Banner and News Items |
| NEWS PHONE | Direct Dial and Telecommunication Network Access to STN |
| NEWS WWW | CAS World Wide Web Site (general information) |

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:06:02 ON 17 JUN 2004

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> FILE REGISTRY

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.42 | 0.42 |

FILE 'REGISTRY' ENTERED AT 13:07:04 ON 17 JUN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 16 JUN 2004 HIGHEST RN 694434-66-7
DICTIONARY FILE UPDATES: 16 JUN 2004 HIGHEST RN 694434-66-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
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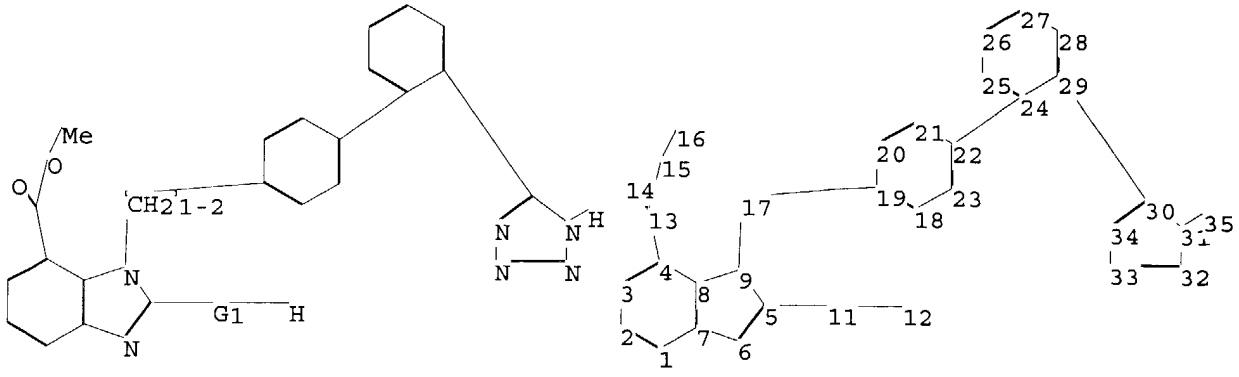



chain nodes :
11 12 13 14 15 16 17 35
ring nodes :
1 2 3 4 5 6 7 8 9 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
chain bonds :
4-13 5-11 9-17 11-12 13-14 13-15 15-16 17-19 22-24 29-30 31-35
ring bonds :
1-2 1-7 2-3 3-4 4-8 5-6 5-9 6-7 7-8 8-9 18-19 18-23 19-20 20-21 21-22 22-23 24-25 24-29 25-26 26-27 27-28 28-29 30-31 30-34 31-32 32-33 33-34

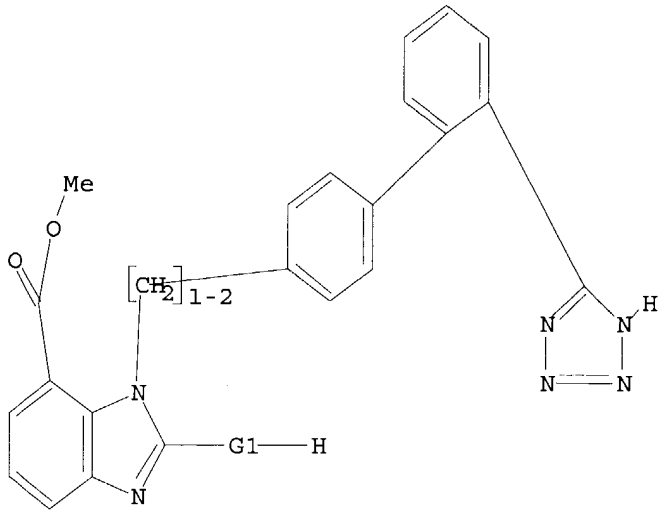
exact/norm bonds :
5-6 5-9 5-11 6-7 8-9 11-12 13-14 13-15 30-31 30-34 31-32 32-33 33-34
exact bonds :
4-13 9-17 15-16 17-19 22-24 29-30 31-35
normalized bonds :
1-2 1-7 2-3 3-4 4-8 7-8 18-19 18-23 19-20 20-21 21-22 22-23 24-25 24-29 25-26 26-27 27-28 28-29
isolated ring systems :
containing 1 : 18 : 24 : 30 :

G1:O,S,N

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:Atom 19:Atom 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom 32:Atom 33:Atom 34:Atom 35:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR




G1 O,S,N

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED -      4 TO ITERATE

100.0% PROCESSED       4 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            4 TO      200
PROJECTED ANSWERS:               0 TO        0

L2             0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 13:07:33 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    112 TO ITERATE

100.0% PROCESSED     112 ITERATIONS                            12 ANSWERS
SEARCH TIME: 00.00.01

L3            12 SEA SSS FUL L1

=> FIL CAPLUS
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               155.42     155.84

FILE 'CAPLUS' ENTERED AT 13:07:38 ON 17 JUN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 17 Jun 2004 VOL 140 ISS 25
FILE LAST UPDATED: 16 Jun 2004 (20040616/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 6 L3

=> s l3/p
L5 5 L3/P

=> s l4 and py<=1990
13515463 PY<=1990
L6 0 L4 AND PY<=1990

=> d l6 ibib abs hitstr tot
L6 HAS NO ANSWERS
'IBIB ABS HITSTR ' IS NOT A VALID STRUCTURE FORMAT KEYWORD
Structure Formats
SIA ----- Structure Image, Attributes, and map table if it contains data. (Default)
SIM ----- Structure IMage.
SAT ----- Structure ATtributes and map table if it contains data.
SCT ----- Structure Connection Table and map table if it contains data.
SDA ----- All Structure DAta (image, attributes, connection table and map table if it contains data).
NOS ----- NO Structure data.
ENTER STRUCTURE FORMAT (SIA), SCT, SDA, SIM, SAT, NOS:end

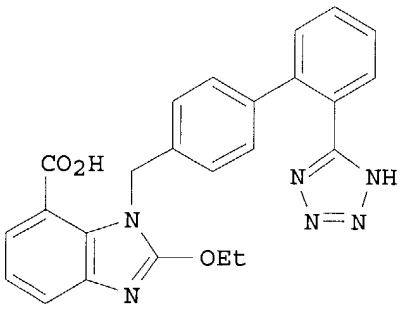
=> d l5 ibib abs hitstr tot

L5 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:133265 CAPLUS
DOCUMENT NUMBER: 138:170242
TITLE: Preparation of crystals of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid and process for producing the same
INVENTOR(S): Hashimoto, Hideo; Maruyama, Hideaki
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003014112 | A1 | 20030220 | WO 2002-JP7861 | 20020801 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1420016 | A1 | 20040519 | EP 2002-758782 | 20020801 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| JP 2003113180 | A2 | 20030418 | JP 2002-225642 | 20020802 |

PRIORITY APPLN. INFO.: JP 2001-236802 A 20010803
WO 2002-JP7861 W 20020801

GI




I

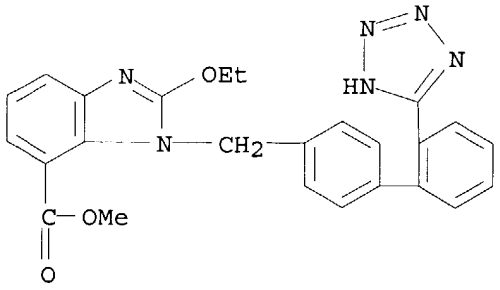
AB Disclosed is a process for producing crystals of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (I), characterized by dissolving or suspending the compound I or a salt thereof in a solvent comprising an aprotic polar solvent and crystallizing it. By the process, the impurities which are contained in the compound I or its salt and are difficult to remove, such as tin compds., analogs of the compound I, and a residual organic solvent, can be easily removed. Crystals of the compound I can be efficiently and easily mass-produced in high yield on an industrial scale. The compound I is useful as an angiotensin II inhibitor for the treatment of diseases induced by angiotensin II or a factor induced by angiotensin II, or diseases induced by angiotensin II receptor-mediated vascular contraction and proliferation and organ disorders, e.g. hypertension and heart diseases. Thus, 5.0 g I (preparation given), 6 mL THF, and 6 mL H2O were mixed, dissolved, stirred with 0.15 g activated charcoal for .apprx.30 min, filtered, followed by washing the charcoal with a mixture of THF and H2O (9:1) (10 mL), and the filtrate and the washing were combined, treated dropwsie with 87.5 mL H2O, and stirred for .apprx.1 h. The precipitated crystals were separated, washed with 20 mL THF/H2O (2:3), and dried to give 4.5 g I (90% yield) containing 0.08% ketone, 0.06% ester, 3,780 ppm THF, and ≤0.6 ppm Sn.

IT **139481-69-9P**, Methyl 1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-

yl)methyl]-2-ethoxybenzimidazole-7-carboxylate
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis to free acid)

RN 139481-69-9 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:779811 CAPLUS
DOCUMENT NUMBER: 130:53943
TITLE: Production of aminobenzene compounds with improved worker safety
INVENTOR(S): Hashimoto, Hideo; Hanaoka, Tadashi; Kato, Masayasu
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 31 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 881212 | A1 | 19981202 | EP 1998-109211 | 19980520 |
| EP 881212 | B1 | 20011031 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| US 6177587 | B1 | 20010123 | US 1998-80456 | 19980519 |
| AT 207884 | E | 20011115 | AT 1998-109211 | 19980520 |
| ES 2162367 | T3 | 20011216 | ES 1998-109211 | 19980520 |
| CA 2238427 | AA | 19981126 | CA 1998-2238427 | 19980525 |
| CN 1203223 | A | 19981230 | CN 1998-101894 | 19980525 |
| JP 11043474 | A2 | 19990216 | JP 1998-142653 | 19980525 |
| JP 3003030 | B2 | 20000124 | | |

PRIORITY APPLN. INFO.: JP 1997-134195 A 19970526
OTHER SOURCE(S): MARPAT 130:53943
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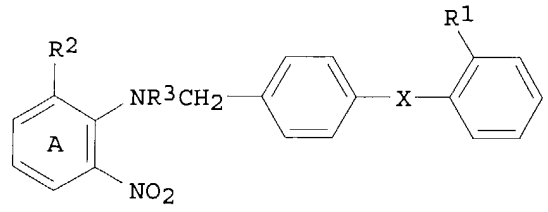

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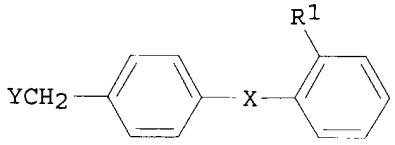

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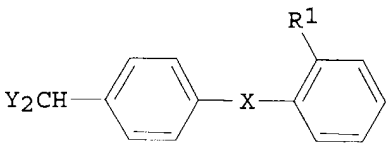
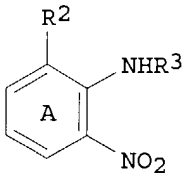


III



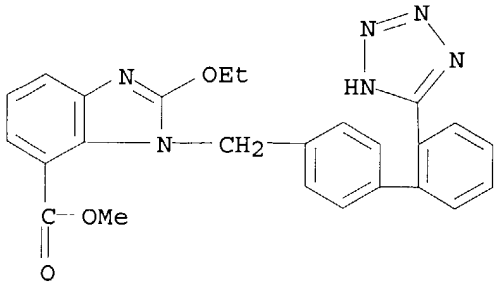
IV

AB Aminobenzene compds. I (R1, R2 are groups capable of forming an anion; R3 = acyl; X = bond, spacer of 1-2 atoms; A is a benzene ring which may have addnl. optional substituents) are prepared by reacting a mixture of a monohalogen compound II (Y is a halogen) and dihalogen compound III with an aminobenzene IV. The I are easily produced in in good yield in a completely airtight system, avoiding worker exposure to mutagenic II and salts thereof, and are useful as synthetic intermediates for the production of medicines.

IT **139481-69-9P**
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of; in production of aminobenzene compds. with improved worker safety)

RN 139481-69-9 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

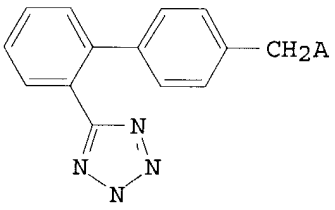
ACCESSION NUMBER: 1994:270821 CAPLUS
DOCUMENT NUMBER: 120:270821
TITLE: Tri-higher alkyl tin azide and its use
INVENTOR(S): Kato, Takeshi; Shida, Yasushi
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 578125 | A1 | 19940112 | EP 1993-110458 | 19930630 |
| EP 578125 | B1 | 19980401 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| US 5484955 | A | 19960116 | US 1993-83697 | 19930629 |
| AT 164584 | E | 19980415 | AT 1993-110458 | 19930630 |
| ES 2113975 | T3 | 19980516 | ES 1993-110458 | 19930630 |
| CA 2099822 | AA | 19940107 | CA 1993-2099822 | 19930705 |
| CA 2099822 | C | 20031216 | | |
| JP 06073028 | A2 | 19940315 | JP 1993-166639 | 19930706 |
| JP 2990566 | B2 | 19991213 | | |
| JP 06073029 | A2 | 19940315 | JP 1993-166640 | 19930706 |
| US 5599943 | A | 19970204 | US 1995-519717 | 19950828 |

PRIORITY APPLN. INFO.: JP 1992-178484 A 19920706
US 1993-83697 A3 19930629

OTHER SOURCE(S): MARPAT 120:270821
GI

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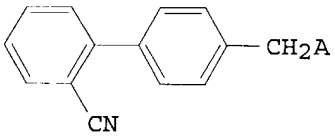
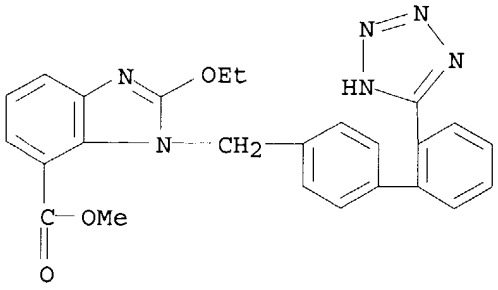


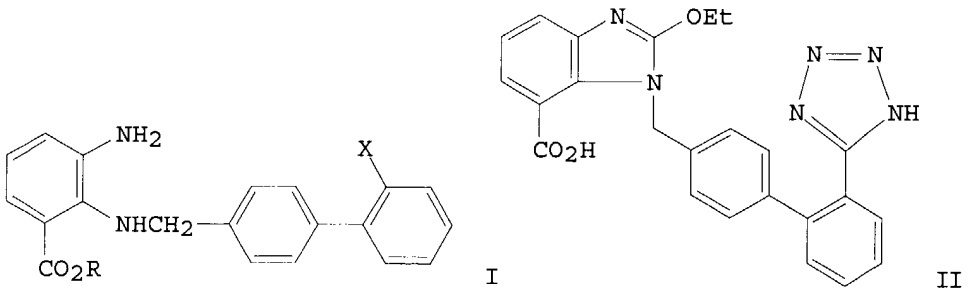

II

AB Disclosed are a compound of the formula (R)3SnN3, wherein R is a C7-18 alkyl, and a process for producing a tetrazolylbenzene compd.of formula I (A = H, phthalimido group) which comprises reacting a cyanobenzene compound, e.g., II with a (R)3SnN3. This process is useful for a safe and com. profitable production of the tetrazolylbenzene compound which is employed for producing a tetrazole derivative having a hypotensive action based on angiotensin II-antagonizing activity or a production intermediate thereof.

IT **139481-69-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 139481-69-9 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:560184 CAPLUS
DOCUMENT NUMBER: 119:160184
TITLE: Nonpeptide angiotensin II receptor antagonists. Synthesis and biological activity of benzimidazolecarboxylic acids
AUTHOR(S): Kubo, Keiji; Kohara, Yasuhisa; Imamiya, Eiko; Sugiura, Yoshihiro; Inada, Yoshiyuki; Furukawa, Yoshiyasu; Nishikawa, Kohei; Naka, Takehiko
CORPORATE SOURCE: Pharm. Res. Div., Takeda Chem. Ind., Ltd., Osaka, 532, Japan
SOURCE: Journal of Medicinal Chemistry (1993), 36(15), 2182-95
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

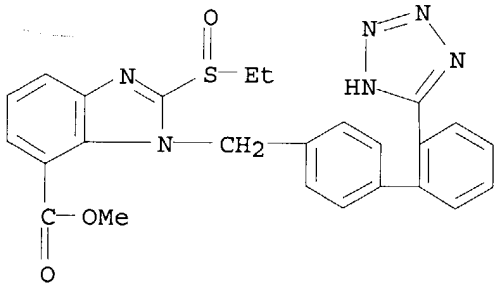


I II

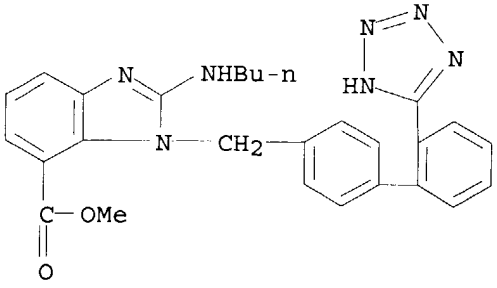
AB A series of 2-substituted-1-(biphenyl-4-ylmethyl)-1H-benzimidazole-7-carboxylic acids was prepared from the key intermediate 3-amino-2-[(biphenyl-4-ylmethyl)amino]benzoate I (R = Me, Et, X = CN, R = Me, X = CO2Me) in order to clarify the structure-activity relationships of various analogs of 2-butyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (CV-11194), a potent and long acting angiotensin II (AII) receptor antagonist. The AII antagonistic activity of the benzimidazoles was investigated by in vitro assays, which included an AII receptor binding assay and AII-induced vasocontraction assay, as well as by in vivo assays such as an AII-induced pressor response in rats. Most of the benzimidazoles showed high affinity for the AII receptor (IC50 value, 10-6-10-7 M) and inhibited the AII-induced pressor response at 1 or 3 mg/kg po, and the effects were more potent than those of CV-11194 and DuP753. The structure-activity relationship studies on the binding affinity and the inhibition of AII-induced pressor response suggested that

straight chains of a certain length (e.g., ethoxy groups, Et groups) were the best as substituents at the 2-position and that their steric factors, lipophilicity, and electronic effects affected the potency of the AII antagonistic action. Both a carboxyl group at the 7-position and a tetrazole ring at the 2'-position were particularly important for potent and orally active AII antagonistic activity and a long-acting hypotensive effect. The representative compound, 2-ethoxy-1-[[2-(1H-tetrazol-5-yl)biphenyl]-4-ylmethyl]-1H-benzimidazole-7-carboxylic acid (CV-11974) (II), inhibited the specific binding of [125I]AII to bovine adrenal cortical membrane with an IC50 value of 1.1 + 10-7 M. The AII-induced contraction of rabbit aortic strips was antagonized by CV-11974 (IC50 value, 3.0 + 10-10 M). Oral administration of CV-11974 to conscious normotensive rats at 1 mg/kg resulted in long-lasting inhibition of the AII-induced pressor response. CV-11974 at 0.1-1 mg/kg i.v. reduced blood pressure dose-dependently in spontaneously hypertensive rats.

IT **150058-22-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and angiotensin II receptor antagonist activity of)
RN 150058-22-3 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylsulfinyl)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)

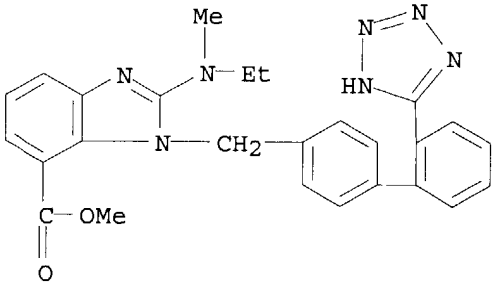


IT **139481-96-2P 139481-99-5P 139482-05-6P 150058-20-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and saponification of)
RN 139481-96-2 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(butylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)

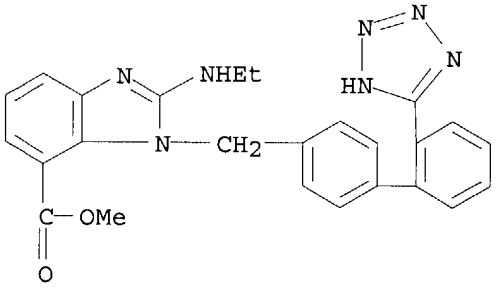


RN 139481-99-5 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylmethylamino)-1-[[2'-(1H-

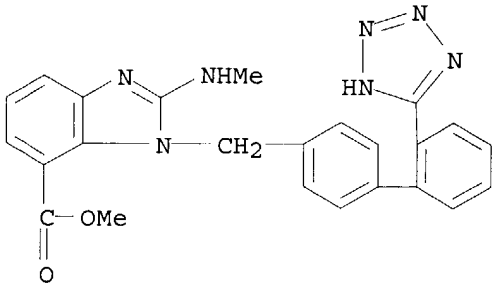
tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



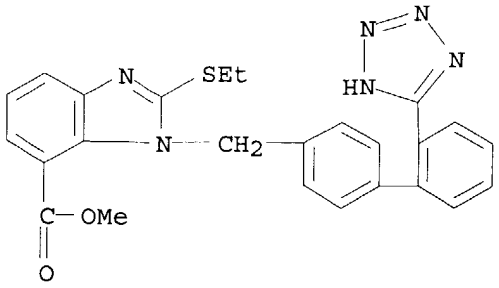
RN 139482-05-6 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



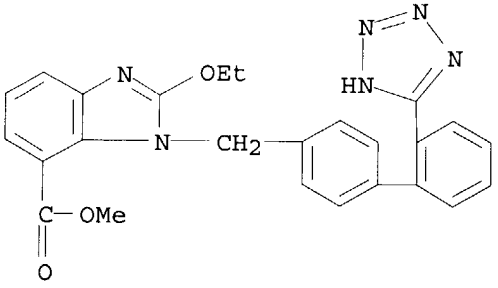
RN 150058-20-1 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(methylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



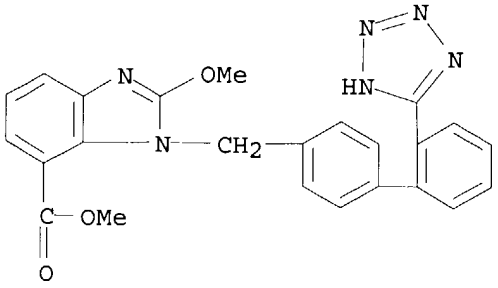
IT **150058-21-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, hydrolysis, and angiotensin II receptor antagonist activity of)
RN 150058-21-2 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylthio)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



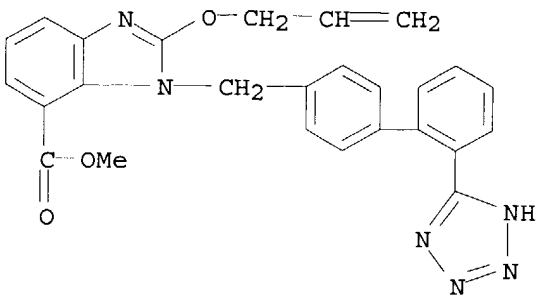
IT **139481-69-9P 139481-75-7P 139481-94-0P**
**139481-95-1P 139482-06-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, saponification, and angiotensin II receptor antagonist activity of)
RN 139481-69-9 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



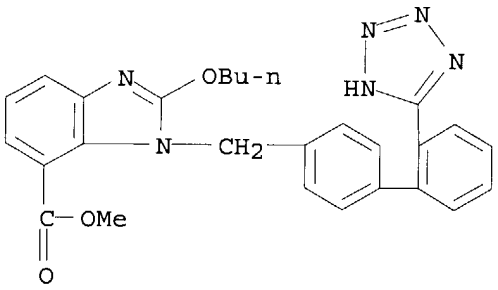
RN 139481-75-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-methoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



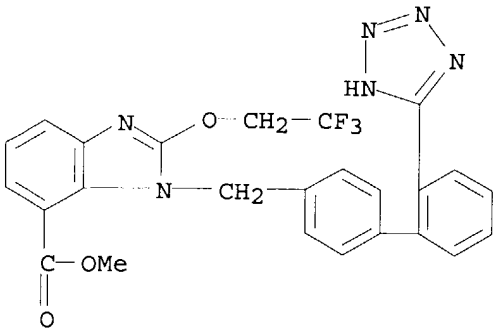
RN 139481-94-0 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(2-propenyloxy)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



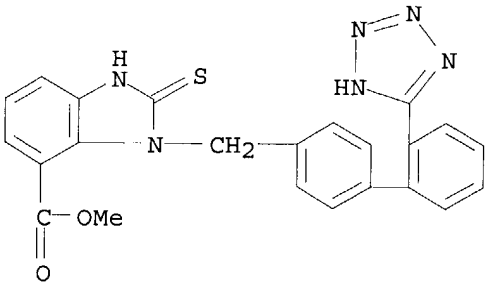
RN 139481-95-1 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-butoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 139482-06-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2-(2,2,2-trifluoroethoxy)-, methyl ester (9CI) (CA INDEX NAME)



IT **150058-19-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, saponification, and methylation of)
RN 150058-19-8 CAPLUS
CN 1H-Benzimidazole-4-carboxylic acid, 2,3-dihydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2-thioxo-, methyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:128924 CAPLUS
DOCUMENT NUMBER: 116:128924
TITLE: Preparation of benzimidazole derivatives as angiotensin II antagonists
INVENTOR(S): Naka, Takehiko; Nishikawa, Kohei; Kato, Takeshi
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 70 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 459136 | A1 | 19911204 | EP 1991-106330 | 19910419 |
| EP 459136 | B1 | 19961227 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| IL 97882 | A1 | 19961114 | IL 1991-97882 | 19910416 |
| US 5196444 | A | 19930323 | US 1991-687238 | 19910418 |
| EP 720982 | A1 | 19960710 | EP 1995-118796 | 19910419 |
| EP 720982 | B1 | 20021113 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| AT 146779 | E | 19970115 | AT 1991-106330 | 19910419 |
| ES 2095266 | T3 | 19970216 | ES 1991-106330 | 19910419 |
| AT 227709 | E | 20021115 | AT 1995-118796 | 19910419 |
| ES 2181742 | T3 | 20030301 | ES 1995-118796 | 19910419 |
| CA 2040955 | AA | 19911028 | CA 1991-2040955 | 19910422 |
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| NO 9101586 | A | 19911028 | NO 1991-1586 | 19910422 |
| ZA 9102983 | A | 19920129 | ZA 1991-2983 | 19910422 |
| JP 04364171 | A2 | 19921216 | JP 1991-189614 | 19910422 |
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| CA 2204290 | C | 20011218 | CA 1991-2204290 | 19910422 |
| CN 1055927 | A | 19911106 | CN 1991-102569 | 19910423 |
| CN 1048486 | B | 20000119 | | |
| AU 9175331 | A1 | 19911121 | AU 1991-75331 | 19910423 |
| AU 647469 | B2 | 19940324 | | |
| HU 57736 | A2 | 19911230 | HU 1991-1347 | 19910423 |
| HU 213266 | B | 19970428 | | |
| RU 2052455 | C1 | 19960120 | RU 1991-4895495 | 19910423 |
| PL 168958 | B1 | 19960531 | PL 1991-292174 | 19911025 |
| PL 169116 | B1 | 19960628 | PL 1991-308620 | 19911025 |
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| CZ 289405 | B6 | 20020116 | CZ 1991-3239 | 19911025 |
| SK 282473 | B6 | 20020205 | SK 1991-3239 | 19911025 |
| LV 10258 | B | 19950420 | LV 1992-567 | 19921230 |
| US 5328919 | A | 19940712 | US 1993-997703 | 19930105 |
| LT 3246 | B | 19950425 | LT 1993-438 | 19930319 |
| US 5401764 | A | 19950328 | US 1993-58739 | 19930510 |
| US 5705517 | A | 19980106 | US 1993-131667 | 19931005 |
| JP 08099960 | A2 | 19960416 | JP 1995-220844 | 19950829 |
| JP 2853611 | B2 | 19990203 | | |
| CN 1147515 | A | 19970416 | CN 1996-107765 | 19960523 |
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| US 5703110 | A | 19971230 | US 1996-715100 | 19960917 |
| NO 9700195 | A | 19970116 | NO 1997-195 | 19970116 |
| US 5962491 | A | 19991005 | US 1997-924919 | 19970908 |
| FI 9802761 | A | 19981221 | FI 1998-2761 | 19981221 |
| US 6004989 | A | 19991221 | US 1999-280094 | 19990329 |
| US 6232334 | B1 | 20010515 | US 1999-376494 | 19990818 |
| US 2001047020 | A1 | 20011129 | US 2001-817231 | 20010327 |
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| US 2002151723 | A1 | 20021017 | US 2002-46189 | 20020116 |
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PRIORITY APPLN. INFO.:

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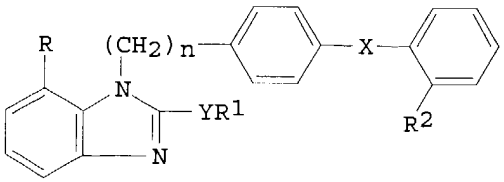
|---|---|---|
| JP 1990-113148 | A | 19900427 |
| JP 1990-141942 | A | 19900530 |
| JP 1990-208662 | A | 19900806 |
| JP 1990-264579 | A | 19901001 |
| JP 1990-413679 | A | 19901224 |
| JP 1992-141942 | A | 19900530 |
| US 1991-687238 | A3 | 19910418 |
| EP 1991-106330 | A3 | 19910419 |
| CA 1991-2040955 | A3 | 19910422 |
| FI 1991-1936 | A3 | 19910422 |
| JP 1991-189614 | A | 19910422 |
| US 1993-997703 | A3 | 19930105 |
| US 1993-58739 | A3 | 19930510 |
| US 1993-131667 | A3 | 19931005 |
| US 1996-715100 | A3 | 19960917 |
| US 1997-924919 | A3 | 19970907 |
| US 1999-280094 | A3 | 19990329 |
| US 1999-376494 | A3 | 19990818 |
| US 2001-817231 | A3 | 20010327 |
| US 2002-46189 | A3 | 20020116 |

OTHER SOURCE(S): MARPAT 116:128924
GI



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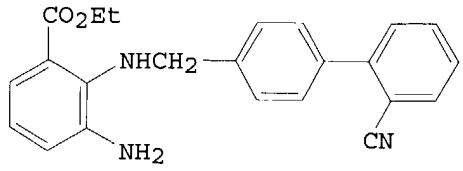


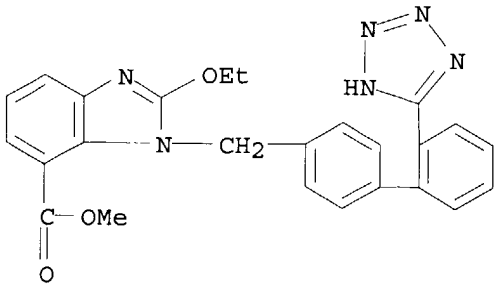
II

AB Benzimidazole derivs. [I; R = (esterified) CO2H, CONH2, a group capable of forming an anion; R1 = H, (substituted) hydrocarbyl; R2 = a group capable of forming an anion; X = bond, spacer of 1 or 2 atoms; Y = O, S(O)m (m = 0, 1, 2), NR4 = H, (substituted) alkyl; n = 1, 2], useful in treating hypertension, heart diseases, etc., are prepared HOAc was added to a solution of ester II in C(OMe)4 with stirring at 80° to give 90% I (R = CO2Et, YR1 = OMe, R2 = cyano, X = bond, n = 1). Also prepared were 58 addnl. I, which showed up to 96% inhibition of angiotensin II binding at 10-6M in a radioreceptor assay.

IT **139481-69-9P 139481-75-7P 139481-94-0P 139481-95-1P 139481-96-2P 139481-99-5P 139482-05-6P 139482-06-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as angiotensin II antagonist)

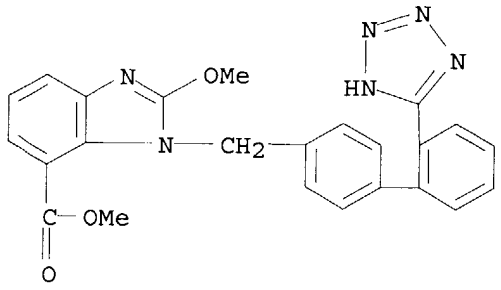
RN 139481-69-9 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)

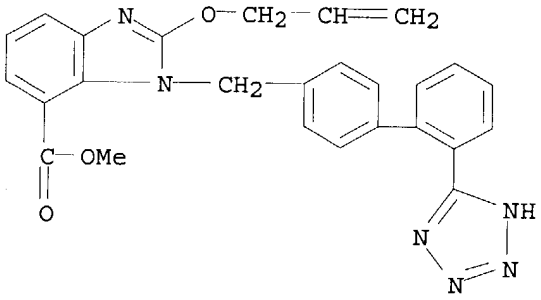


RN 139481-75-7 CAPLUS

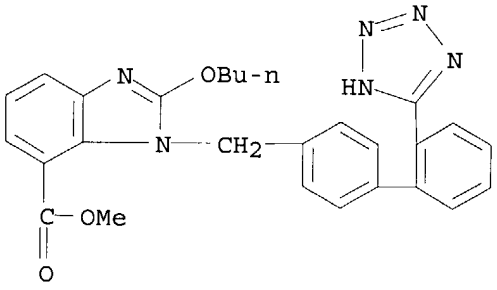
CN 1H-Benzimidazole-7-carboxylic acid, 2-methoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



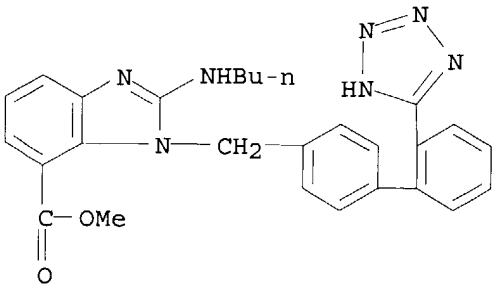
RN 139481-94-0 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(2-propenyloxy)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



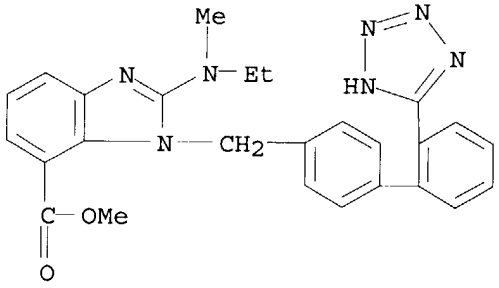
RN 139481-95-1 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-butoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



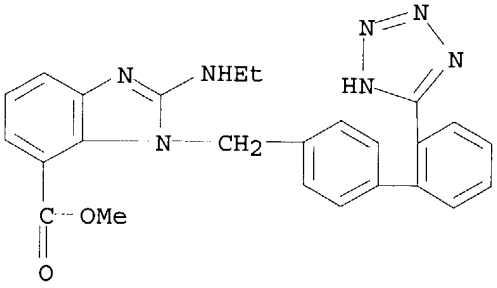
RN 139481-96-2 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(butylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



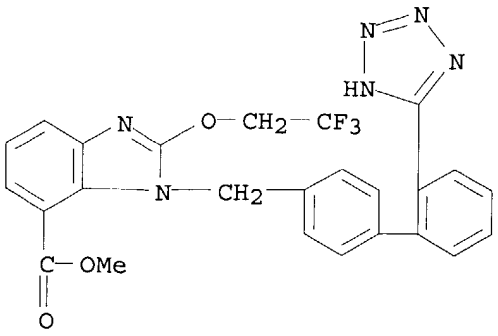
RN 139481-99-5 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylmethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 139482-05-6 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 139482-06-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2-(2,2,2-trifluoroethoxy)-, methyl ester (9CI) (CA INDEX NAME)



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L4 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:133265 CAPLUS
DOCUMENT NUMBER: 138:170242
TITLE: Preparation of crystals of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid and process for producing the same
INVENTOR(S): Hashimoto, Hideo; Maruyama, Hideaki
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003014112 | A1 | 20030220 | WO 2002-JP7861 | 20020801 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1420016 | A1 | 20040519 | EP 2002-758782 | 20020801 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| JP 2003113180 | A2 | 20030418 | JP 2002-225642 | 20020802 |

PRIORITY APPLN. INFO.: JP 2001-236802 A 20010803
WO 2002-JP7861 W 20020801

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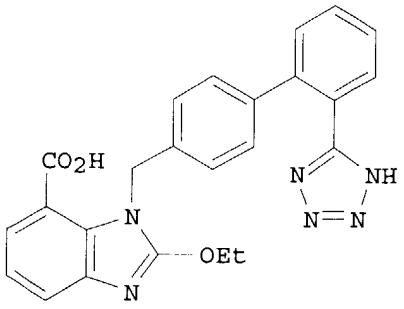


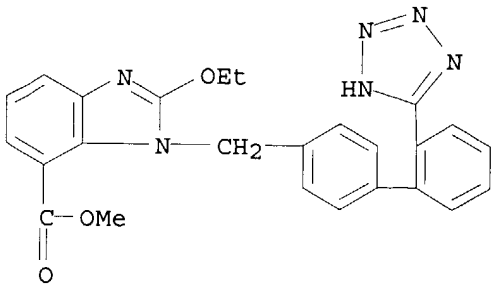
I

AB Disclosed is a process for producing crystals of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (I), characterized by dissolving or suspending the compound I or a salt thereof in a solvent comprising an aprotic polar solvent and crystallizing it. By the process, the impurities which are contained in the compound I or its salt and are difficult to remove, such as tin compds., analogs of the compound I, and a residual organic solvent, can be easily removed. Crystals of the compound I can be efficiently and easily mass-produced in high yield on an industrial scale. The compound I is useful as an angiotensin II inhibitor for the treatment of diseases induced by angiotensin II or a factor induced by angiotensin II, or diseases induced by angiotensin II receptor-mediated vascular contraction and proliferation and organ disorders, e.g. hypertension and heart diseases. Thus, 5.0 g I (preparation given), 6 mL THF, and 6 mL H2O were mixed, dissolved, stirred with 0.15 g activated charcoal for .apprx.30 min, filtered, followed by washing the charcoal with a mixture of THF and H2O (9:1) (10 mL), and the filtrate and the washing were combined, treated dropwsie with 87.5 mL H2O, and stirred for .apprx.1 h. The precipitated crystals were separated, washed with 20 mL THF/H2O (2:3), and dried to give 4.5 g I (90% yield) containing 0.08% ketone, 0.06% ester, 3,780 ppm THF, and ≤0.6 ppm Sn.

IT **139481-69-9P**, Methyl 1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis to free acid)

RN 139481-69-9 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)

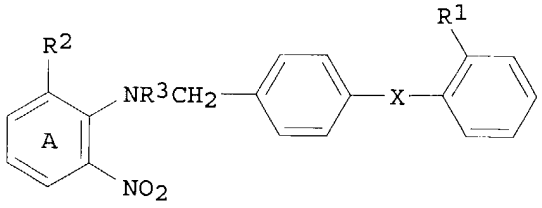


REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

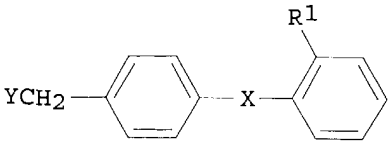
L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:779811 CAPLUS
DOCUMENT NUMBER: 130:53943
TITLE: Production of aminobenzene compounds with improved worker safety
INVENTOR(S): Hashimoto, Hideo; Hanaoka, Tadashi; Kato, Masayasu
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 31 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 881212 | A1 | 19981202 | EP 1998-109211 | 19980520 |
| EP 881212 | B1 | 20011031 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| US 6177587 | B1 | 20010123 | US 1998-80456 | 19980519 |
| AT 207884 | E | 20011115 | AT 1998-109211 | 19980520 |
| ES 2162367 | T3 | 20011216 | ES 1998-109211 | 19980520 |
| CA 2238427 | AA | 19981126 | CA 1998-2238427 | 19980525 |
| CN 1203223 | A | 19981230 | CN 1998-101894 | 19980525 |
| JP 11043474 | A2 | 19990216 | JP 1998-142653 | 19980525 |
| JP 3003030 | B2 | 20000124 | | |

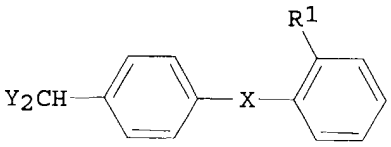
PRIORITY APPLN. INFO.: JP 1997-134195 A 19970526
OTHER SOURCE(S): MARPAT 130:53943
GI



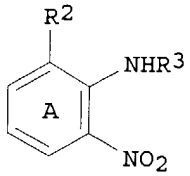

I




II




III



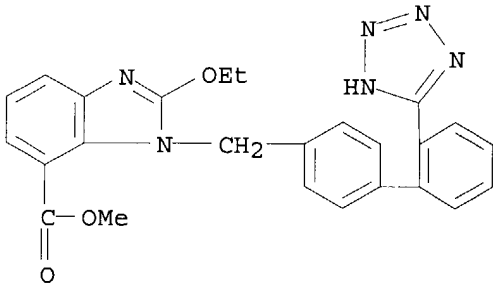

IV

AB Aminobenzene compds. I (R1, R2 are groups capable of forming an anion; R3 = acyl; X = bond, spacer of 1-2 atoms; A is a benzene ring which may have addnl. optional substituents) are prepared by reacting a mixture of a monohalogen compound II (Y is a halogen) and dihalogen compound III with an aminobenzene IV. The I are easily produced in in good yield in a completely airtight system, avoiding worker exposure to mutagenic II and salts thereof, and are useful as synthetic intermediates for the production of medicines.

IT **139481-69-9P**
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of; in production of aminobenzene compds. with improved worker safety)

RN 139481-69-9 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:712908 CAPLUS

DOCUMENT NUMBER: 126:384

TITLE: Synthesis and Angiotensin II Receptor Antagonistic Activities of Benzimidazole Derivatives Bearing Acidic Heterocycles as Novel Tetrazole Bioisosteres

AUTHOR(S): Kohara, Yasuhisa; Kubo, Keiji; Imamiya, Eiko; Wada, Takeo; Inada, Yoshiyuki; Naka, Takehiko

CORPORATE SOURCE: Pharmaceutical Research Divisions, Takeda Chemical Industries Ltd., Osaka, 532, Japan

SOURCE: Journal of Medicinal Chemistry (1996), 39(26), 5228-5235
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

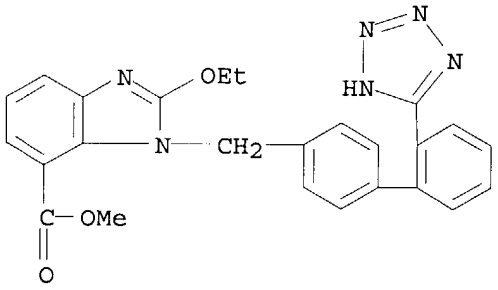
AB The design, synthesis, and biol. activity of benzimidazole-7-carboxylic acids bearing 5-oxo-1,2,4-oxadiazole, 5-oxo-1,2,4-thiadiazole, 5-thioxo-1,2,4-oxadiazole, and 2-oxo-1,2,3,5-oxathiadiazole rings are described. The compds. were evaluated for in vitro and in vivo angiotensin II (AII) receptor antagonistic activities. Most were found to have high affinity for the AT1 receptor (IC50 value, 10-6-10-7M) and to inhibit the AII-induced pressor response (more than 50% inhibition at 1 mg/kg po). The 5-oxo-1,2,4-oxadiazole, 5-oxo-1,2,4-thiadiazole, and 5-thioxo-1,2,4-oxadiazole derivs. showed stronger inhibitory effects than the corresponding tetrazole derivs., while their binding affinities were weaker. This might be ascribed to their improved bioavailability by

increased lipophilicity. This study showed that the 5-oxo-1,2,4-oxadiazole ring and its thio analog, the 5-oxo-1,2,4-thiadiazole ring, could be lipophilic bioisosteres for the tetrazole ring in nonpeptide AII receptor antagonists.

IT **139481-69-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis and angiotensin II receptor antagonistic activities of benzimidazole derivs.)

RN 139481-69-9 CAPLUS

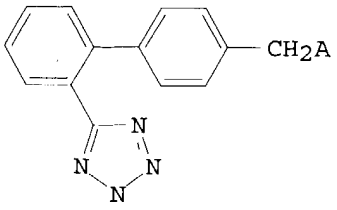
CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



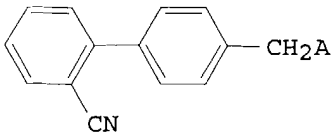
L4 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:270821 CAPLUS
DOCUMENT NUMBER: 120:270821
TITLE: Tri-higher alkyl tin azide and its use
INVENTOR(S): Kato, Takeshi; Shida, Yasushi
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 578125 | A1 | ~~19940112~~ | EP 1993-110458 | 19930630 |
| EP 578125 | B1 | 19980401 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| US 5484955 | A | 19960116 | US 1993-83697 | 19930629 |
| AT 164584 | E | 19980415 | AT 1993-110458 | 19930630 |
| ES 2113975 | T3 | 19980516 | ES 1993-110458 | 19930630 |
| CA 2099822 | AA | 19940107 | CA 1993-2099822 | 19930705 |
| CA 2099822 | C | 20031216 | | |
| JP 06073028 | A2 | 19940315 | JP 1993-166639 | 19930706 |
| JP 2990566 | B2 | 19991213 | | |
| JP 06073029 | A2 | 19940315 | JP 1993-166640 | 19930706 |
| US 5599943 | A | 19970204 | US 1995-519717 | 19950828 |

PRIORITY APPLN. INFO.: JP 1992-178484 A 19920706
US 1993-83697 A3 19930629
OTHER SOURCE(S): MARPAT 120:270821
GI




I



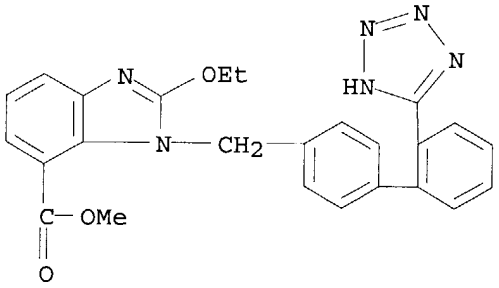

II

AB Disclosed are a compound of the formula (R)3SnN3, wherein R is a C7-18 alkyl, and a process for producing a tetrazolylbenzene compd.of formula I (A = H, phthalimido group) which comprises reacting a cyanobenzene compound, e.g., II with a (R)3SnN3. This process is useful for a safe and com. profitable production of the tetrazolylbenzene compound which is employed for producing a tetrazole derivative having a hypotensive action based on angiotensin II-antagonizing activity or a production intermediate thereof.

IT **139481-69-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 139481-69-9 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)




L4 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1993:560184 CAPLUS

DOCUMENT NUMBER: 119:160184

TITLE: Nonpeptide angiotensin II receptor antagonists. Synthesis and biological activity of benzimidazolecarboxylic acids

AUTHOR(S): Kubo, Keiji; Kohara, Yasuhisa; Imamiya, Eiko; Sugiura, Yoshihiro; Inada, Yoshiyuki; Furukawa, Yoshiyasu; Nishikawa, Kohei; Naka, Takehiko

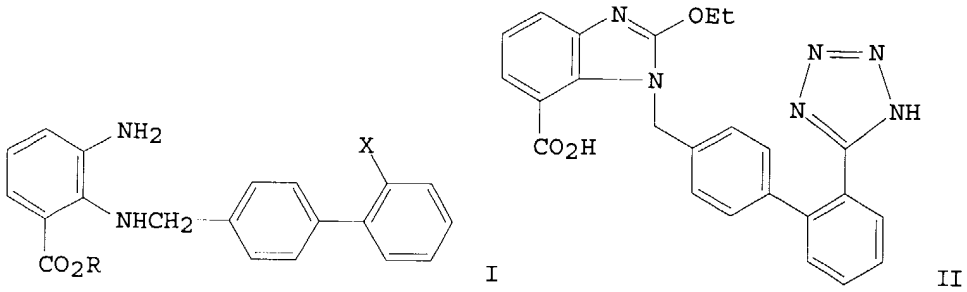
CORPORATE SOURCE: Pharm. Res. Div., Takeda Chem. Ind., Ltd., Osaka, 532, Japan

SOURCE: Journal of Medicinal Chemistry (1993), 36(15), 2182-95
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

GI

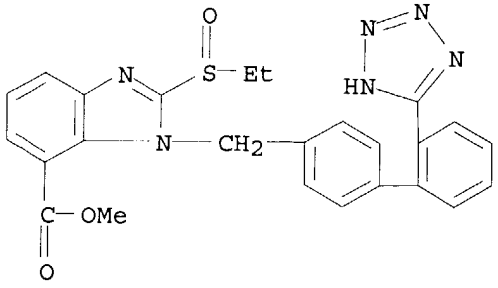



AB A series of 2-substituted-1-(biphenyl-4-ylmethyl)-1H-benzimidazole-7-carboxylic acids was prepared from the key intermediate 3-amino-2-[(biphenyl-4-ylmethyl)amino]benzoate I (R = Me, Et, X = CN, R = Me, X = CO2Me) in order to clarify the structure-activity relationships of various analogs of 2-butyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (CV-11194), a potent and long acting angiotensin II (AII) receptor antagonist. The AII antagonistic activity of the benzimidazoles was investigated by in vitro assays, which included an AII receptor binding assay and AII-induced vasocontraction assay, as well as by in vivo assays such as an AII-induced pressor response in rats. Most of the benzimidazoles showed high affinity for the AII receptor (IC50 value, 10-6-10-7 M) and inhibited the AII-induced pressor response at 1 or 3 mg/kg po, and the effects were more potent than those of CV-11194 and DuP753. The structure-activity relationship studies on the binding affinity and the inhibition of AII-induced pressor response suggested that straight chains of a certain length (e.g., ethoxy groups, Et groups) were the best as substituents at the 2-position and that their steric factors, lipophilicity, and electronic effects affected the potency of the AII antagonistic action. Both a carboxyl group at the 7-position and a tetrazole ring at the 2'-position were particularly important for potent and orally active AII antagonistic activity and a long-acting hypotensive effect. The representative compound, 2-ethoxy-1-[[2-(1H-tetrazol-5-yl)biphenyl]-4-ylmethyl]-1H-benzimidazole-7-carboxylic acid (CV-11974) (II), inhibited the specific binding of [125I]AII to bovine adrenal cortical membrane with an IC50 value of 1.1 + 10-7 M. The AII-induced contraction of rabbit aortic strips was antagonized by CV-11974 (IC50 value, 3.0 + 10-10 M). Oral administration of CV-11974 to conscious normotensive rats at 1 mg/kg resulted in long-lasting inhibition of the AII-induced pressor response. CV-11974 at 0.1-1 mg/kg i.v. reduced blood pressure dose-dependently in spontaneously hypertensive rats.

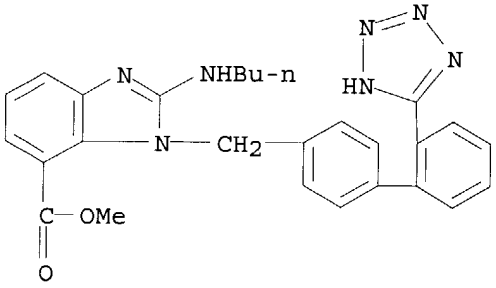
IT **150058-22-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and angiotensin II receptor antagonist activity of)

RN 150058-22-3 CAPLUS

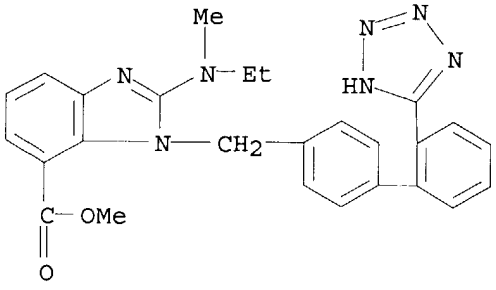
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylsulfinyl)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



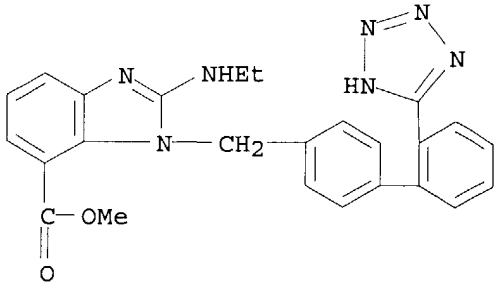
IT **139481-96-2P 139481-99-5P 139482-05-6P 150058-20-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and saponification of)
RN 139481-96-2 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(butylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



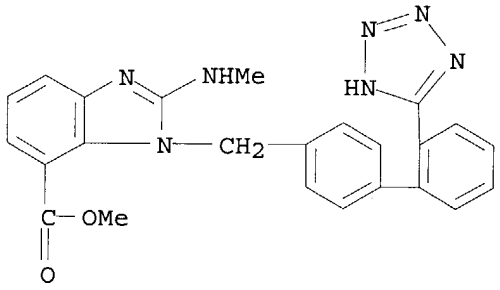
RN 139481-99-5 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylmethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



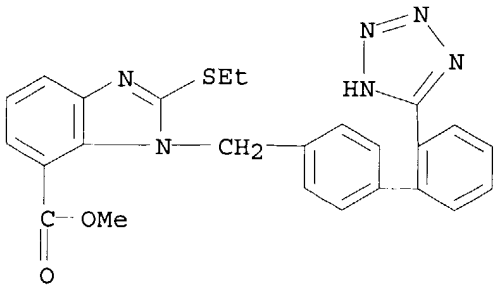
RN 139482-05-6 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 150058-20-1 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(methylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)

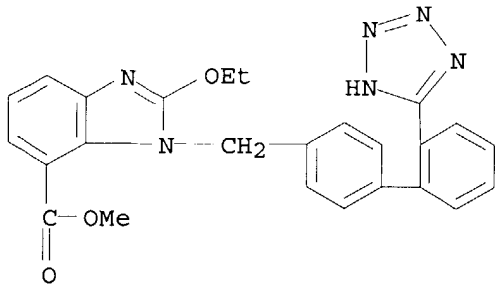


IT **150058-21-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, hydrolysis, and angiotensin II receptor antagonist activity of)
RN 150058-21-2 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylthio)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)

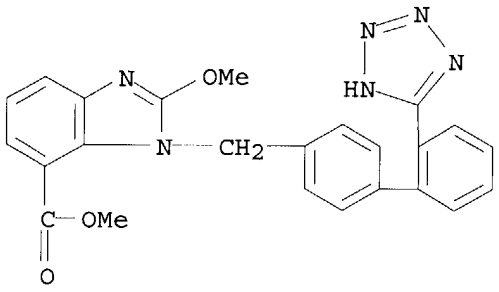


IT **139481-69-9P 139481-75-7P 139481-94-0P**
**139481-95-1P 139482-06-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, saponification, and angiotensin II receptor antagonist activity of)
RN 139481-69-9 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-

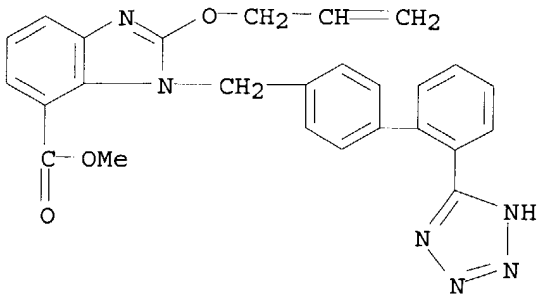
yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



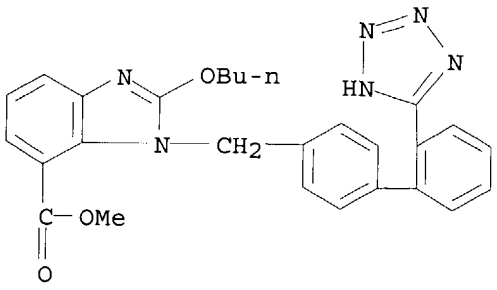
RN 139481-75-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-methoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



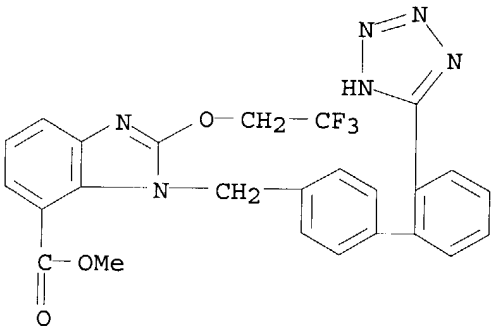
RN 139481-94-0 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(2-propenyloxy)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



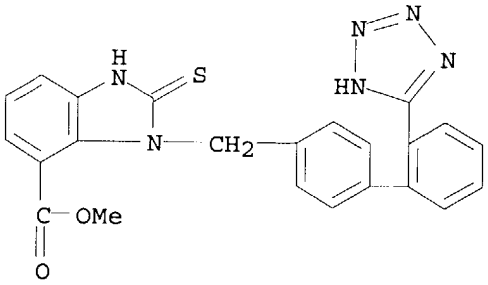
RN 139481-95-1 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-butoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 139482-06-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2-(2,2,2-trifluoroethoxy)-, methyl ester (9CI) (CA INDEX NAME)



IT **150058-19-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, saponification, and methylation of)
RN 150058-19-8 CAPLUS
CN 1H-Benzimidazole-4-carboxylic acid, 2,3-dihydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2-thioxo-, methyl ester (9CI) (CA INDEX NAME)



L4 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:128924 CAPLUS
DOCUMENT NUMBER: 116:128924
TITLE: Preparation of benzimidazole derivatives as

angiotensin II antagonists
INVENTOR(S): Naka, Takehiko; Nishikawa, Kohei; Kato, Takeshi
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 70 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 459136 | A1 | 19911204 | EP 1991-106330 | 19910419 |
| EP 459136 | B1 | 19961227 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| IL 97882 | A1 | 19961114 | IL 1991-97882 | 19910416 |
| US 5196444 | A | 19930323 | US 1991-687238 | 19910418 |
| EP 720982 | A1 | 19960710 | EP 1995-118796 | 19910419 |
| EP 720982 | B1 | 20021113 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| AT 146779 | E | 19970115 | AT 1991-106330 | 19910419 |
| ES 2095266 | T3 | 19970216 | ES 1991-106330 | 19910419 |
| AT 227709 | E | 20021115 | AT 1995-118796 | 19910419 |
| ES 2181742 | T3 | 20030301 | ES 1995-118796 | 19910419 |
| CA 2040955 | AA | 19911028 | CA 1991-2040955 | 19910422 |
| CA 2040955 | C | 19980203 | | |
| NO 9101586 | A | 19911028 | NO 1991-1586 | 19910422 |
| ZA 9102983 | A | 19920129 | ZA 1991-2983 | 19910422 |
| JP 04364171 | A2 | 19921216 | JP 1991-189614 | 19910422 |
| JP 2514282 | B2 | 19960710 | | |
| CA 2204290 | C | 20011218 | CA 1991-2204290 | 19910422 |
| CN 1055927 | A | 19911106 | CN 1991-102569 | 19910423 |
| CN 1048486 | B | 20000119 | | |
| AU 9175331 | A1 | 19911121 | AU 1991-75331 | 19910423 |
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| HU 57736 | A2 | 19911230 | HU 1991-1347 | 19910423 |
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| PL 169451 | B1 | 19960731 | PL 1991-308621 | 19911025 |
| PL 170324 | B1 | 19961129 | PL 1991-308619 | 19911025 |
| CZ 289405 | B6 | 20020116 | CZ 1991-3239 | 19911025 |
| SK 282473 | B6 | 20020205 | SK 1991-3239 | 19911025 |
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| LT 3246 | B | 19950425 | LT 1993-438 | 19930319 |
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| FI 2001002172 | A | 20011109 | FI 2001-2172 | | 20011109 |
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| US 6608210 | B2 | 20030819 | | | |
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| JP 1990-113148 | A | 19900427 |
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| JP 1990-208662 | A | 19900806 |
| JP 1990-264579 | A | 19901001 |
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| JP 1992-141942 | A | 19900530 |
| US 1991-687238 | A3 | 19910418 |
| EP 1991-106330 | A3 | 19910419 |
| CA 1991-2040955 | A3 | 19910422 |
| FI 1991-1936 | A3 | 19910422 |
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| US 1993-997703 | A3 | 19930105 |
| US 1993-58739 | A3 | 19930510 |
| US 1993-131667 | A3 | 19931005 |
| US 1996-715100 | A3 | 19960917 |
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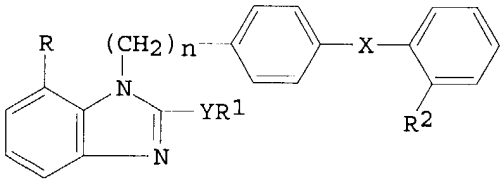
| US 1999-376494 | A3 | 19990818 |
| US 2001-817231 | A3 | 20010327 |
| US 2002-46189 | A3 | 20020116 |

OTHER SOURCE(S): MARPAT 116:128924


GI

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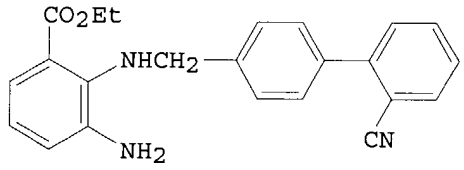


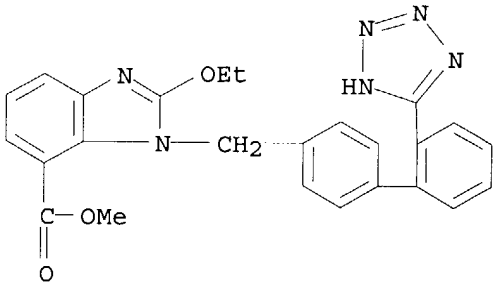

II


AB Benzimidazole derivs. [I; R = (esterified) CO2H, CONH2, a group capable of forming an anion; R1 = H, (substituted) hydrocarbyl; R2 = a group capable of forming an anion; X = bond, spacer of 1 or 2 atoms; Y = O, S(O)m (m = 0, 1, 2), NR4 = H, (substituted) alkyl; n = 1, 2], useful in treating hypertension, heart diseases, etc., are prepared HOAc was added to a solution of ester II in C(OMe)4 with stirring at 80° to give 90% I (R = CO2Et, YR1 = OMe, R2 = cyano, X = bond, n = 1). Also prepared were 58 addnl. I, which showed up to 96% inhibition of angiotensin II binding at 10-6M in a radioreceptor assay.

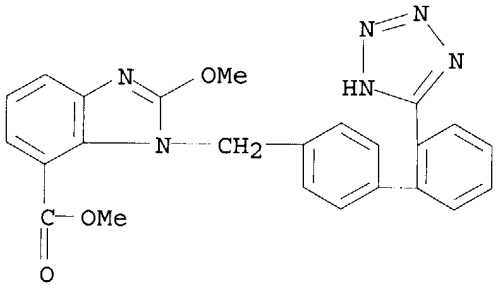

IT **139481-69-9P 139481-75-7P 139481-94-0P**
**139481-95-1P 139481-96-2P 139481-99-5P**
**139482-05-6P 139482-06-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as angiotensin II antagonist)

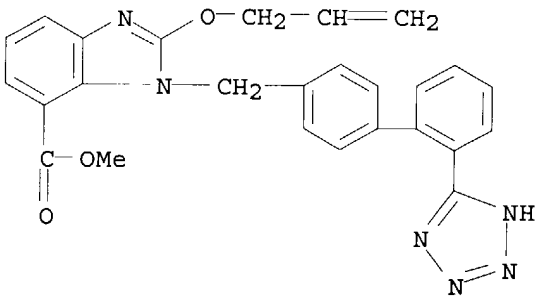
RN 139481-69-9 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



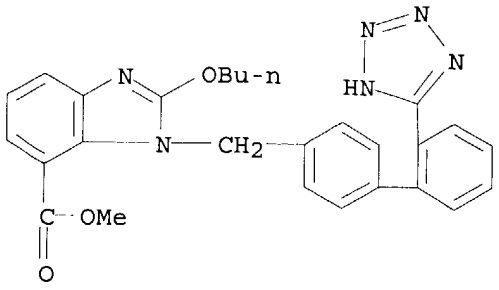
RN 139481-75-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-methoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



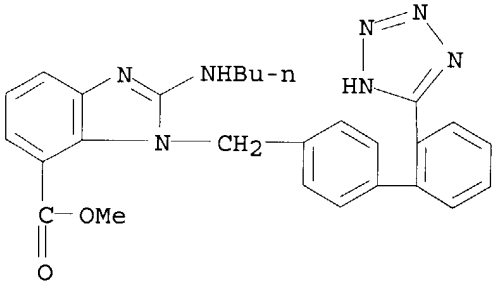
RN 139481-94-0 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(2-propenyloxy)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



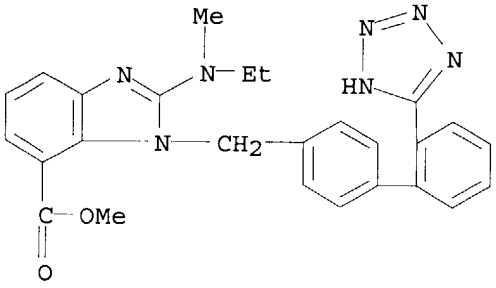
RN 139481-95-1 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-butoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



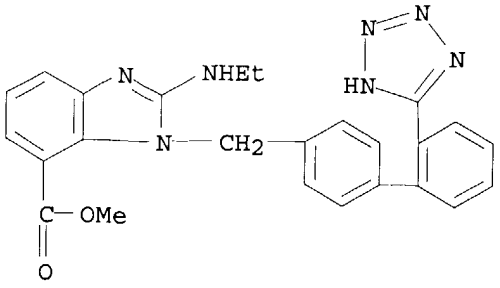
RN 139481-96-2 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(butylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



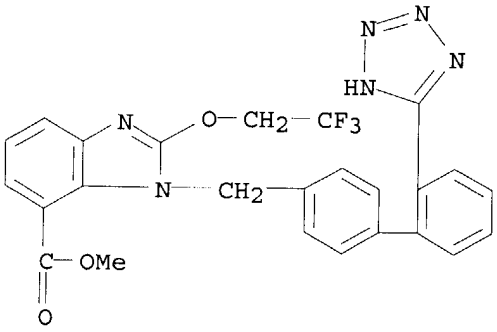
RN 139481-99-5 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylmethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 139482-05-6 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 139482-06-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2-(2,2,2-trifluoroethoxy)-, methyl ester (9CI) (CA INDEX NAME)



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| FULL ESTIMATED COST | 55.89 | 211.73 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -7.62 | -7.62 |

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